Pharmacopoeas in France after the French revolution

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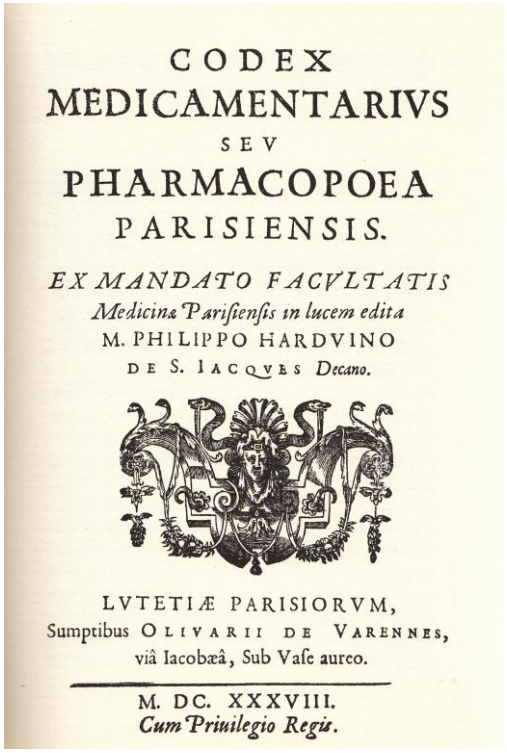
Introduction

The word 'pharmacopoeia' covers several documents, relatively different from one period to another, and also from country to country. The recent French *Dictionnaire de l'Académie nationale de Pharmacie* (http://dictionnaire.acadpharm.org) defines it as 'originally, the art of preparing drugs, then a book compiling drugs in use at a given period of time, often described as a Codex; currently, an official register, regularly revised by a scientific commission, published in a given country, or in several countries, and which imposes norms for pharmaceutical activities'. With that definition it can be seen that the content, the format, and the legal environment of their use, as well as the geographical area covered by the pharmacopoeias, changed over time, their application being sometimes limited to a specific region. Reference documents and pharmaceutical formularies were used as long ago as the Sumerian civilization and in Ancient Egypt.

If some authors consider that the first Codex was published in Florence (Italy) in 1498, under the name of *Nuevo receptario*, apothecaries from Paris had to possess Nicolas' Antidote book after 1332. Several other reference books were published from the 16th to the 18th centuries, including the *Promptuaire des simples médecines en rhitme joyeuse* of Thibault Lespleigney, as well as the Pharmacopoeias of Moyse Charas in 1676 and of Nicolas Lémery in 1697. The Parisian Pharmacopoeia (*Codex Medicamentarius seu Pharmacopoea Parisiensis*) was published in Latin from 1638 to the last edition in 1758, and was then the unofficial pharmaceutical guide for the whole French Kingdom. The French Pharmacopoeia (*Pharmacopée française)*, now official for the whole country, was published 60 years later, in 1818, also in Latin under the title *Codex Medicamentarius, sive Pharmacopoea Gallica*. It is this edition that will be considered here, with its following editions, as well as reference books that were published at the same period during the 19th and 20th centuries.



CODEX
MEDICAMENTARIVS
SEV
PHARMACOPOEA
PARISIENSIS.

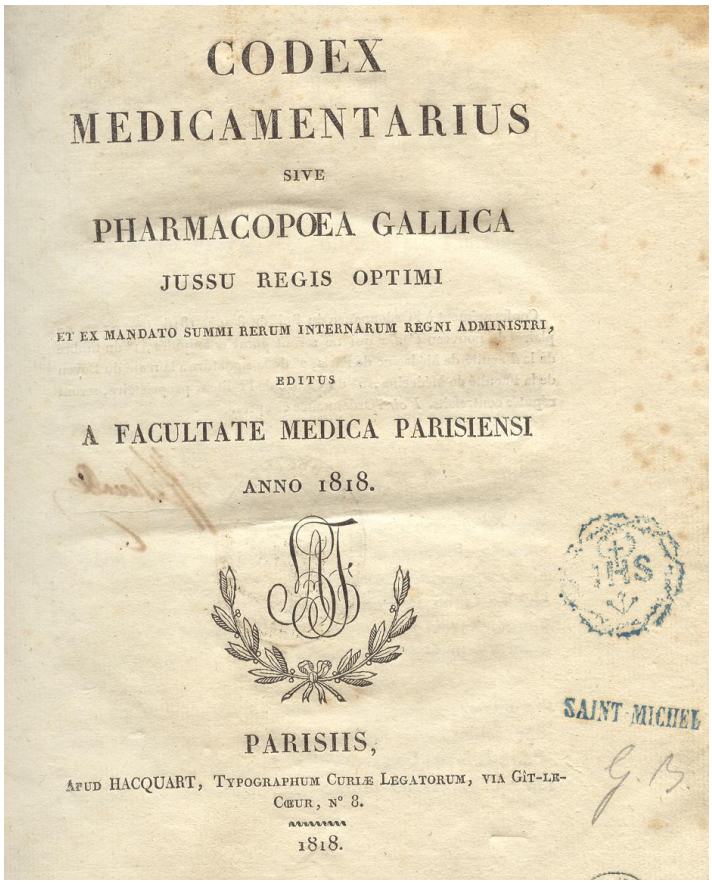
EX MANDATO FACVLTATIS
Medicinæ Parisiensis in lucem edita
M. PHILIPPO HARDVINO
DE S. IACQVES Decano.

LVTETIÆ PARISIORVM,
Sumptibus OLIVARII DE VARENNES,
viâ Iacobæâ, Sub Vase aureo.

M. DC. XXXVIII.
Cum Priuilegio Regis.

The 1818 Pharmacopoeia: context and comments

During the years between the *Parisian Pharmacopoeia* in 1758 and the *French Pharmacopoeia* in 1818, political regimes were changing rapidly; they included the pre-Revolution period, the French Revolution, Empire, and Restoration. From a scientific point of view, Lavoisier and the new chemistry were slowly infiltrating the scientific community. The new Codex was being prepared, since the Germinal Law of year XI (1803) indicated that: 'The Government will ask professors of medicine, jointly with members of the schools of pharmacy, to write a Codex or Formulary that will contain medical and pharmaceutical preparations that should be in the hands of all pharmacists. This Formulary will have to include sufficient different preparations to be adapted to climate and production differences according to the different parts of the French territory; it will be published only with the authorization of the French Government and according to its orders'.


CODEX
MEDICAMENTARIUS
SIVE
PHARMACOPŒA GALLICA
JUSSU REGIS OPTIMI
ET EX MANDATO SUMMI RERUM INTERNARUM REGNI ADMINISTRI,
EDITUS
A FACULTATE MEDICA PARISIENSI
ANNO 1818.
SAINT-MICHEL
PARISIIS,
APUD HACQUART, TYPOGRAPHUM CURIÆ LEGATORUM, VIA GIT-LE-CŒUR, N° 8.
1818.

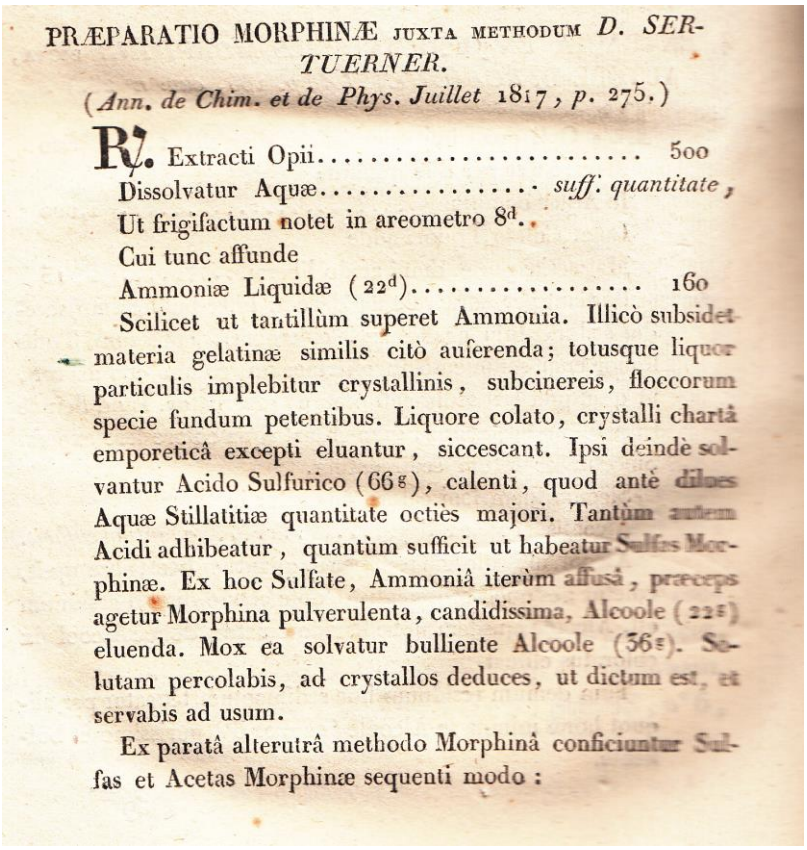
This objective of the Government of year XI was not put in effect immediately, and some signs of impatience were observed. In 1816 for example, even though he had not been authorized to do so, the prefect of Bas-Rhin region asked the director of the School of Medicine to designate a commission, including members of that School in association with the School of Pharmacy, with orders 'to publish a new Formulary and an associated price list'. Another pharmacopoeia was finalized in Angers in 1812, but the School of Pharmacy of Paris considered that, since a Codex of drugs was under preparation according to the 1803 law, it was appropriate 'to stop the publication of specific pharmacopoeias that we would like to publish'.

In 1816 a Royal Ordinance was published relating to the Codex which obliged the Home Office to publish and to print this Codex, and indicating that the pharmacists would have to possess this Codex in the six months period following its publication (if they did not they would be prosecuted). However, it would be necessary to wait for two more years before the final publication! Finally, the Royal Ordinance specified that each copy would not only be stamped with the stamp of the Faculty

of Medicine of Paris, but also hand-written with the signature of the Dean of the Faculty of Medicine and the monogram of the editor.

Basically, the French Codex of 1818 was not innovative. First of all, for the language used: Latin. The first version in Latin was translated, one year later, into French. But it is said the 'the edition in Latin is the only official edition recognized by the Government: it is that edition that has to be in the hands of pharmacists'. Several other translations were published in 1819, 1821, 1826 and 1827 respectively, with or without comments and additional notes. It was necessary to wait for the 1837 edition, in French only, to recognize the usage of French for that Pharmacopoeia.

The first edition of the Codex of 1818 included 636 pages and was divided in two parts: *materia medica* and compositions. *Materia medica* took 223 pages and was sub-divided in drugs coming from the mineral kingdom (66 raw materials), the vegetable kingdom (818 herbs), and the animal kingdom (36 drugs). We can find also equivalence between the old measures and the new metric system, the physical measures (weight, temperatures, etc). We can see for example that 35° Reaumur, equivalent to 43.37°C, is the temperature that is usually observed to drink tea and other hot drinks, information that remains in the Codex of 1837. The second part of the book is divided into ten sections with several chapters: these give details of the processes used for the preparation of raw materials (fermentation, extraction, distillation, for example), but also chemical drugs. In the appendices of the Codex, we can find the way to prepare morphine and emetine, recently isolated. Among synthetized products, are found artificial mineral waters: 'eau acidule carbonique', Vichy's waters, Seltz's, Sedlitz's, Balaruc's waters, and so on. But with these modern products for the time, there are also several very old and traditional compositions. Theriac is one of them with the formula of the 1758 *Parisian Pharmacopoeia*. We can also find earthworm oil, viper, frog, or lizard stocks, etc.



PRÆPARATIO MORPHINÆ JUXTA METHODUM *D. SERTUERNER.*

(*Ann. de Chim. et de Phys. Juillet* 1817, *p.* 275.)

℞. Extracti Opii..... 500
Dissolvatur Aquæ..... *suff. quantitate*,
Ut frigifactum notet in areometro 8d..
Cui tunc affunde
Ammoniæ Liquidæ (22d)..... 160
Scilicet ut tantillùm superet Ammonia. Illicò subsidet materia gelatinæ similis citò auferenda; totusque liquor particulis implebitur crystallinis, subcinereis, floccorum specie fundum petentibus. Liquore colato, crystalli chartâ emporeticâ excepti eluantur, siccescant. Ipsi deindè solvantur Acido Sulfurico (66g), calenti, quod antè dilues Aquæ Stillatitiæ quantitate octiès majori. Tantùm autem Acidi adhibeatur, quantùm sufficit ut habeatur Sulfas Morphinæ. Ex hoc Sulfate, Ammoniâ iterùm affusâ, præceps agetur Morphina pulverulenta, candidissima, Alcoole (22g) eluenda. Mox ea solvatur bulliente Alcoole (36g). Solutam percolabis, ad crystallos deduces, ut dictum est, et servabis ad usum.

Ex paratâ alterutrâ methodo Morphinâ conficiuntur Sulfas et Acetas Morphinæ sequenti modo :

The introduction to the 1818 Codex shows that pharmacists were clearly involved in the writing of the document, especially Henry, at that time director of the Central Pharmacy of Paris' hospitals, who was particularly concerned with alcoholic and ethereal tinctures. But also involved were Vauquelin, Deyeux, Bouillon-Lagrange and Chéradame. However, as soon as it was published, and also during several of the following years, many criticisms were made of this Codex that was now the mandatory reference work.

First of all, the format was criticized. Latin had been used, apparently, to reduce the access of drugs to quacks! As Jourdan wrote in his translation of the Codex in 1821, it is not French versions of medical texts which increase the numbers and confidence of quacks. 'They prefer to take the formulations of their so-called mysteries in old compendiums of recipes that they change in a mysterious manner to sell them at a higher price to the public'. Also concerning the format, an article in the *Journal de Pharmacie et des sciences accessoires* of 1819 criticized the chosen classification and ranking of formulations. 'It is not obvious, at first glance, to understand why whey is found in the pulps and starches section: why syrups are in the same section as alcoholic tinctures, ethers are close to mineral waters and soaps', etc. Finally, there was criticism that the title of the book was given in Latin: some would have preferred the title Pharmacopoea *francorum* rather that *Gallica,* since French people of the early 19th century were not from the same blood as Gauls fighting against Romans!

The second area of concerns discussed in the pages of the *Journal de Pharmacie* after publication of the Codex related to the editor and its cost. Having a monopoly for the sales of the book, as the pharmacists were obliged to buy it, the price of Pharmacopoeia, edited by Mr. Hacquart, was considered too expensive (18 francs at that time), or even as a disguised tax! This editor, a few years later, would go to court to fight against a Doctor Virey, who included in his book *Traité de Pharmacie théorique et pratique,* published in 1819, several formulations of the recently published Codex. This claim for breach of copyright would be rejected by the courthouses.

The third aspect of criticisms of the 1818 Pharmacopoeia was related to the content itself. Very quickly and as soon as 1819, the *Journal de Pharmacie* published hundreds of criticisms: some products which correspondents thought should be lincluded were missing, such as chromium 'that should replace the word « gagates » (jayet or jet) that has no interest in pharmacy, and is just good to make jokes'. The description of iron was less than three lines. Conversely, some old words such as colcothar, calamine, tuthie, etc. were found, 'when most important products which have the issue to be new, are hardly mentioned'. More generally, criticisms were made about the insufficient and vague descriptions. For *materia medica*, authors mentioned that 'Doctor Virey intends to criticize in details that part of the Codex, very neglected part that seems to have been written quickly, if one does not remember the huge time used to prepare this document and the number of long conferences, meetings, discussions and thoughts of scientists, teachers and academicians that are at the origin of the French Pharmacopoeia'.

Concerning formulations that were included in the second part of the Codex 'one finds classification of drugs as wrong and vicious'. Also, some monographs were wrong or incomplete. To take one example, the Pharmacopoeia included two processes to isolate ricin oil. One critic asked: 'Why these two processes? They are not equally good. The best one should have been indicated and filtration should have been recommended to separate more rapidly mucilage which, when present, accelerates oil to go rancid. This precaution should be applied to all extractions of oils'. There were also forgotten items like Sarsaparilla simple syrup which was 'one of the most used: one looks in vain for that composition in the Codex'. All the critics of the 1819 Codex concluded with the statement that

the editor should not be surprised about there being little willingness amongst pharmacists to buy this book, even if they were under threat of a 500 fr. fine.

When Jourdan published the French version, he added that 'nitrous acid seems to us a useless formulation… ; corrosive sublimate and calomel being chlorides should not be named muriates in the Codex', and so on. In 1827, Ratier published a new translation of the *French Pharmacopoeia* where he added some comments and complementary notes of Henry the son. A new translation was also published the same year by Jourdan, reviewed, corrected and increased by A. Fée, a pharmacist and member of the Royal Academy of Medicine, where he protested against errors that were present in the 1818 edition of *Codex medicamentarius* and 'regrets that this book did not meet the needs of the public, based on an appropriated fame.' Finally, in 1831, Adolphe Buisson wrote his thesis on the Pharmaceutical Codex, and focussed on the huge number of criticisms that could be made of it.

The following editions of the French Codex

As was said in the 1837 edition of the *French Pharmacopoeia*, 'it is in the nature of Codex or Pharmacopeias to age quickly, and to have then a need to be frequently renewed'. It was then necessary to publish new revised and corrected editions that were taking into account the scientific progresses and criticisms of previous versions. Planche tells us that in 1835 a new Commission was put in charge of a revision of Codex and soon, he hoped, 'France will have a pharmaceutical code, able, as our Civil Code, to serve as a model for neighboring peoples'. It would be done in 1837, and then in 1866, 1884, 1908 (completed by a supplement in 1920, and also in 1926 and 1933), in 1937 (with a supplement in 1947), in 1949, 1965, 1972, 1983 and finally in 2012 (11th edition).

With each successive edition, new items were added, as well as deletions taking place, such as theriac which was finally deleted in 1908. We can see also the improvement in the definition of a drug. In the 1866 edition, a drug is defined as 'any substance which is introduced in the economy in order to treat a disease status'. Drugs are consequently items of commerce. But the pharmacists gave the title 'drug' to every substance included in the Codex, as being part of the *materia medica;* to every formulation, as a result of it being either an official formula appearing in an official formulary, or being a formulation prescribed by a physician. Generally speaking, the term was applied to any simple or composed product that the pharmacist had to prepare on request, and that had to be administered to cure a disease status.

The introduction also makes clear the difference between a drug and a remedy, this last term being 'everything that can fight against a disease, improve patient status, obtain a cure of disease: bleeding, electricity, hydrotherapy, regimes, are all remedies; emetic, quinine sulfate, chloroform, are drugs'. Along the successive editions, chemistry and synthetic active ingredients take up increasing space. The idea that the *French Pharmacopoeia* might be a pharmacopeia that is valid for several countries, or even universal as dreamed by Lemery, is more and more discussed. As early as 1866, one part is dedicated to formulations coming from foreign pharmacopoeias.

We can see also the development of analytical tests, and identification methods (mainly after 1908) which allow to better qualify purity of products and also to identify falsifications of drugs. The qualification of some items as 'poisonous products' takes place after 1884, as does the appearance of veterinary products. The edition of 1908 indicates the creation of inspectors in pharmacy, but also maximum dosages to be used for some drugs. We can find in addition a number of essential laws for the exercise of pharmacy. The edition of 1937, very delayed because of the First World War, allows us to see for the first time vaccines and serums, and to increase the place of biological products. Also, it is the first time to mention the tablet form (comprimé). The labeling of drugs, already mentioned in previous editions, is reinforced for toxic substances. The 1947 supplement includes sulphonamides,

and common denominations of drugs, only suggested in the 1937 edition. The 1949 edition is for the first time published by the *Ordre des Pharmaciens,* created in 1945. But it is mainly the first introduction of antibiotics, and the use of radioactive probes for treatment or diagnostic purpose, as well as a number of new monographs, that characterize this 1949 edition. As for previous editions, it is stated that the *French Pharmacopoeia* is not only constituted by the last edition but also by all previous ones.

In 1965, the new version of the Codex is prepared under the direction of professor Guillaume Valette, president of the Permanent Commission of Pharmacopoeia. A number of chemical drugs replace simple drugs of the vegetable kingdom. But the main innovation this time is the introduction of homeopathy in order to define rigorously the preparation of mother tinctures, macerates, etc. Analytical methods are also reinforced and are part of the 1965 pharmacopoeia. In addition, it is the first mention of containers and accessories in plastic and type A glass vials (borosilicated glass) and type B glass (sodocalcic surface treated glass) that will become types I and II glasses after 1972. Interestingly, a new chapter is introduced about products used in Oenology. We should not forget that, in the wine-growing regions at that time, acidity and alcoholic degree analysis were made by pharmacists at request of wine-producers. Faced with the increasing work needed to keep the *French Pharmacopoeia* regularly updated, when new scientific information and products were growing at a fast rate, the Ministry of Health (Service Central de la Pharmacie), with the support of several parts of the profession, decided to create in 1965 an *Association for the technical and scientific evolution of research applied to Pharmacopoeia* (ADRAPHARM) (1901 law association) : its objective was to obtain public and private fundings to give research grants for updating and verifying experimentally monographs before publication. Later on, in the 1980's, ADRAPHARM took the place of the "Ordre des Pharmaciens" to realize the publication of the pharmacopoeia.

For the IXth edition of the Codex, introduced by Pierre Malangeau in 1972, in order to include the new European pharmacopoeia monographs when available and to replace the corresponding national ones, it was decided to publish the Pharmacopoeia incrementally in the form of small separate leaflets that would be published between 1972 to 1976. These would be added to three supplements, to be published in 1978, 1979 and 1980. The opportunity was also taken at the same time to publish separately the first *National Formulary (1974)*, which would be more dedicated to officinal preparations. Indeed, the new development of European construction (common market needing harmonization of national norms of pharmacopeias) was being inserted into the publication of the French Pharmacopoeia and its updates. The, the first published volume of the European pharmacopoeia for which many French experts where working on, appeared in 1969, with an obligation on all countries to take it into account, and hence for some *European Pharmacopoeia* norms to be included in the French Codex. We can find also a number of new molecules. But what most characterizes this edition is the evolution of the industrial production of drugs, which progressively replaces magisterial preparations, and also internationalization of the pharmaceutical industry. Following the exponential change of the industrial production of drugs, the Pharmacopoeia becomes a cluster of norms and standards for the industry, reducing the interest of a Formulary that becomes an appendix to the Codex. It follows the evolution of the profession and is less and less tailored to the needs of the pharmacists in town. Then, it is not mandatory anymore for them to have in hand the Codex, starting from the Xth edition, but the quality norms of drugs has still to be fulfilled.

In the most recent French Pharmacopoeia (XIth edition published in 2012), only 36 compositions are still present in the National Formulary. In addition, the contribution played by the *European Pharmacopeia* has been considerably increased. More than 3000 monographs and chapters are now common to 37 European countries that signed the Convention.

Despite the efforts for Harmonization through the ICH process between pharmaceutically developed countries, the attempts to obtain a universal pharmacopeia is not yet a success today, some interesting points have to be mentioned:

- WHO has published, under the name of International pharmacopoeia, a compendium of quality norms and methods that are recommended for the analysis of some products and pharmaceutical preparations which are supposed to be used as models for Members state of countries under development.
- A "groupe de discussion des pharmacopées" (Pharmacopoeial Discussion Group), in parallel and now jointly with the ICH process, harmonizes prospectively and also retrospectively existing European/National monographs and chapters.

The other so called pharmacopoeias during the XIXth and XXth centuries

It is tempting to think that the publication of the *French Pharmacopoeia* in 1818, a mandatory reference document for all pharmacists, would have suppressed the need for other reference documents and non-official pharmacopoeias. However, this was not so. On the contrary: the full list would be too large to write here, but we can recall first the book of Doctor Virey already mentioned, *Traité complet de pharmacie théorique et pratique*, published for the first time in 1811, but then edited again regularly after 1818, in 1819 and again 1823. We can also report the Formulary by Cadet de Gassicourt in 1822, and the one from Ratier in 1823. The Cadet de Gassicourt's Formulary was regularly re-edited, and the seventh edition was published in 1833.

Even more significant is the Pharmacopoeia of Henry et Guibourt, published in 1828, and then in 1833 and 1841. In this last edition, we understand that the *French Pharmacopoeia* does not meet the need of pharmacists. It is not sufficiently exhaustive and precise, on the one hand, and includes a number of mistakes on the other. Guibourt is in disagreement with the processes included in the Codex for the preparations of quinquina and ratanhia extracts. For the white decoction of Sydenham, Guibourt recommends the use of white bread, although the Codex is using Arabic gum. Guibourt is also opposed to the Codex about alcoholic tinctures, which he considers too concentrated. The author added also some products such as ferruginous chocolate that were not in the official Codex.

Starting in 1840, two references books were published for pharmacists: these were Bouchardat' *Formulary* (the first edition of which was published in 1840, followed by 36 further editions) and the *Officine* from Dorvault (published for the first time in 1844) for which we have 23 editions. In addition there were a very large number of specialized other books: veterinary drugs, homeopathic drugs, military formularies, news drugs, new specialties (Vidal dictionary), etc., that were published during the course of the 19th and 20th centuries. All of them complemented and sometimes contradicted the *French Pharmacopoeia* of that time.

Conclusion

When looking at the evolution of the *French Pharmacopoeia* from 1818 to today, we have to observe that this reference book, mandatory from regulatory point of view, for all branches of the profession for quality control of production and norms applicable to drugs and API (Active Pharmaceutical Ingredient) used to prepare them, does not cover all aspects of pharmacy. As a result of its limited content, of the mistakes that were made, and of rapidly changing scientific and legal information, it is clear that the Codex, word that disappeared after de 1972 edition, was always running behind scientific progress. Its indisputable merit has been to harmonize the composition of formulations and quality norms, legally mandatory, to fight against charlatanism. Nowadays, the *French Pharmacopoeia* is a sum of norms and standards, methods and reference products, API, excipients,

and reactants, rather than the sum of preparations or formulas for a given drug. The industrialization of the drugs also probably pushes in that direction, driving to specific regulations related to the market authorization where are described appropriated specifications for each specialty. In the new regulations, the pharmacopoeia is still the mandatory reference and harmonization of pharmaceutical forms (i.e. some worldwide harmonized trials between ICH and WHO) and numerous API. If the norms of pharmacopoeia remain the mandatory legal basis for the producer, they are limitative and have to be adapted and completed for each case (i.e. certificate of compliance to the Pharmacopoeia for API, Drug Master File, etc.) Concerning the use of a drug by the prescriber or the patient, it is then the Summary of Product Characteristics (SPC) which is legally a valid reference for a given drug and is mandatory for the producer and the Marketing authorization holder.

Today it is always feasible for the industry to go out of official methods as long as they can justify their choices on a validated scientific background. Nevertheless, harmonization of quality standards is still the common goal, and transnational pharmacopoeias are rapidly moving in that direction to reach the objective. But it remains difficult to ensure that all countries accept the same quality standards and the same way to examine pharmaceutical quality. And it is even more difficult to harmonize the indications and administration protocols from one country to another.

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Four plates of the Codex medicamentarius gallicus of 1936

Pl. III. — Adonis (*Adonis vernalis* L). Renonculacées.

1, rameau fleuri; 2, akène mûr; 3, coupe de la fleur; 4, diagramme. — *Adonis æstivalis* : 5, akène; 6, fleur. — *Adonis autumnalis* : 7, akène.

ABSINTHES

Pl. I. — Grande Absinthe (*Artemisia Absinthium* L.). Synanthérées.
1, rameau fleuri; 2, feuilles de la base; 3, capitule; 4, fleurs femelles tubuleuses; 5, fleur centrale hermaphrodite.

Absinthe marine (*Artemisia maritima* L.). Synanthérées.
6, rameau fleuri; 7, capitule; 8, fleur tubuleuse isolée.

BELLADONE

Pl. XI. — Belladone (*Atropa Belladonna* L.). Solanacées.
1, port de la plante; 2, rameau fleuri avec feuilles géminées; 3, coupe de la fleur; 4, fruit (baie) avec calice persistant; 5, graine; 6, diagramme.